REMARKS

The Office Action dated December 10, 2008 has been carefully considered. Claim 1 is amended to specify that the inventive methods relate to on-chip biopolymer array synthesis as disclosed throughout the application, e.g., paragraphs [0003] and [0005], background of the deficiencies in on-chip quality control, and to narrow the objective to the embodiment requiring "complete deprotection of the amino groups " as disclosed on page 3, paragraph [0005], wherein complete deprotection is taught as essential for the optimal application of the chip. Further support for this embodiment may be found in paragraph [0021] "when no more protecting groups are detected after deprotection, the deprotection has been quantitative, otherwise a repetition of deprotection may be necessary." According to this embodiment, additional deprotection steps are not "optional" if protecting groups are detected; rather, they are "necessary." Claim 13 is amended to specify that the detectable protecting groups are coupled to the nucleotide base through the amine, which is clear by inspection of the structures according to the invention where B is a nucleobase analog having at least one amino group (paragraph [0030]) and as recited in original claim 14. Other changes involve corrections of syntax and other informalities. Since the amendment does not involve new matter, entry is believed warranted and is respectfully requested.

Claims 1-3, 12-13, and 15-22 remain pending and subject to examination.

Rejection under 35 USC §103

The rejection of **claims 1-3, 12, 13, and 15-22** under 35 USC 103(a) as being unpatentable over US Patent No. 6,238,862 to McGall et al (McGall), and Wagner et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997 (Wagner), in view of US Patent No. 5,151,507 to Hobbs et al (Hobbs) and if necessary, Chen et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001; cited previously) and Agris (PGPUB 20020045167; 4/18/2002; cited previously) is maintained for reasons of record in addition to the reasons set forth below. Specifically the Examiner asserts that McGall teaches methods of quality control for manufacturing nucleic acid probe arrays and teaches synthesizing nucleic acids using protected monomers where the protected monomers read on the "detectable protecting groups coupled directly to the building blocks" as recited in claim 1. McGall is also asserted to teach deprotection or removal of the protecting group at the end of each round of synthesis, and the Examiner interprets this to include after the termination of any synthesis step. McGall teaches removal of "photolabile groups" and "side chain protective groups" after the desired products are produced [as will be set forth in detail below, claim 1 is amended to clarify that deprotection does not occur in the instant methods until

synthesis of the entire biopolymer array and does not occur at intermediate synthetic steps as in McGall]. The Examiner further alleges that the reference teaches "determining the amount of unprotected active sites" by detecting the amount of "detectable labels" on the array, and teaches "repeating steps of "deprotection" which assertedly reads on the optionally repeated deprotection step of instant claim 1 [as will be set forth in detail below, the repeating steps of claim 1 are contingent, not optional, i.e., if detection occurs, the deprotection is repeated; if detection does not occur, the deprotection ceases, and in any event complete deprotection is achieved]. According to the Examiner, the reference teaches that the detectable label is a fluorescent label such as a rhodamine, which is linked or coupled to the nucleotide.

The Examiner notes that McGall fails to explicitly teach that the protection groups are directly coupled to and protect the nucleobase amino groups as required by claim 1, and fails to explicitly teach the optional repeating steps of deprotection and detection also as recited in claim 1, and does not teach "stilbene" (the elected species) as the "fluorescent group", as recited in claim 3 or the various chemistries of claims 15-22.

According to the Examiner, however, McGall teaches repeating steps of "deprotection" so that it would be obvious "to optionally repeat both the deprotection and detection steps for the desired results measuring deprotection at different stages" and would have been obvious to one of ordinary skill in the art to apply the standard technique of repeating deprotection and detection steps as the procedure for performing the said steps are taught by McGall, to improve the deprotection (such as to render various degrees of deprotection) and detection (such as to generate an average measurement) for the predicable result of enabling standard oligonucleotide synthesis and the accompanying quality control measurements.

The secondary reference, Wagner, is applied for disclosure of methods of nucleic acid synthesis using protected nucleotides and for the specific teaching wherein a fluorescent label is linked directly to the amino group of the nucleobases, and further teaches detecting the protecting groups attached to the synthesized oligonucleotides as well as deprotecting the label attached nucleobase after the synthesis of the oligonucleotide, e.g., pp. 205-206, figure on pg. 206, which reads on the "at least some of the detectable protecting groups couple directly to amino groups of the building blocks and remained coupled until synthesis terminated" as recited in claim 1. According to the Examiner, Wagner further teaches the structure of nucleotides comprising the various elements of claims 15-22.

The secondary reference, Agris, is applied for allegedly teaching methods of monitoring the degree of deprotection "after" synthesis of oligonucleotides on arrays by detecting detectable protecting

groups "remaining on the array." According to the Examiner, the reference also teaches the need for such detection so that simple and reliable techniques for determining the purity of the desired oligonucleotides can be carried out. Hobbs and Chen are applied for teachings related to various dependent embodiments.

The Examiner concludes that a person of ordinary skill in the art would have been motivated to couple the protection group to the amino group of the nucleobase because the nucleobase protection groups offer the advantages of providing more efficient and fast working oligodeoxyribonucleotide synthesis, as taught by Wagner, and because both the McGall reference and the Wagner reference teach methods of using protected monomers (nucleotide building blocks) to generate oligonucleotides with detection of the degree of deprotection (for either the sugar phosphate groups or the nucleobase groups) that are necessary for completion of oligonucleotide synthesis, it would have been obvious to one skilled in the art to substitute one detection method of detecting the deprotection of the sugar phosphate reactive groups for the other (the deprotection of the nucleobase groups) to achieve the predictable result of determining the degree of deprotection for a solid state oligonucleotide synthesis.

The Examiner further concludes that a person of ordinary skill in the art would be motivated to directly detect the remaining detectable protecting group on an array to assess the purity of the synthesized oligonucleotides "because Agris teaches the need for such as a simple and reliable technique to control the quality of the synthesized microarray, as discussed supra."

This rejection is traversed, and reconsideration is respectfully requested. Applicants respectfully submit that the Examiner fails to grasp the context for the development of the instant inventive methods, and therefore fails to grasp the significance with respect to overcoming the known deficiencies associated with on-chip synthesis of oligonucleotide arrays. Summarily, Applicants assert that the secondary references Wagner and Agris illustrate methods relating to off-chip synthesis of oligonucleotide arrays wherein the practitioner removes the synthesized oligonucleotide for various post-synthetic processing, including assessment of deprotection and purification. In this context, quality control is simple to implement since the oligonucleotides which fail to achieve deprotection may be separated from the fully deprotected oligonucleotides by various affinity, chromatographic, or other column filtration means well-known in the art. The primary reference, McGall, acknowledges and addresses the problems associated with on-chip quality control but develops and discloses an entirely different solution to the problem. If one could simply import the techniques of off-chip synthesis into the context of on-chip synthesis, as the Examiner purports to do by importing the techniques of the secondary references into the method of McGall, the problem of quality control in on-chip synthesis would never have existed to begin with.

Instant claim 1 is directed to a quality control method for achieving complete deprotection of protected reactive groups in on-chip synthesis of a biopolymer array, the method comprising (a) synthesizing a plurality of different oligonucleotide species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks and the detectable protecting groups remain coupled until synthesis of the desired biopolymer array, (b) taking one or more steps to cleave the detectable protecting groups, (c) determining a degree of deprotection by detecting any detectable protecting groups remaining on the array after cleavage, and (d) repeating steps (b) and (c) until detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, wherein the quality control method is performed entirely on-chip.

McGall is the only reference cited by the Examiner that discusses or addresses the problems associated with quality control of chip-bound oligonucleotides, in particular with respect to degree of deprotection. However, McGall provides a different solution than the instant methods and controls the quality of the oligonucleotide chips by deprotecting and testing after each step in synthesis, whereas the instant methods permit a more streamlined quality control. The protecting group is coupled to the nucleobase so that it may remain coupled without interfering with the adding building blocks for synthesis of the full-length oligonucleotide. In McGall, the protecting group is bound to the terminal groups required for the next step in synthesis. The terminal protection groups must be cleaved off before the next step in synthesis takes place. McGall measures the extent of deprotection after each step and must institute multiple quality control correction steps.

In contrast, according to the instant methods the detectable protection groups remain coupled to the oligonucleotide bound to the chip throughout the synthesis of the desired oliogonucleotide array. The addition of each nucleotide building block leads to a proportional increase in fluorescence at each synthetic step so that the instant methods provide the additional advantage of permitting on-line confirmation of the length of the oligonucleotide. Such control is not possible in the methods of McGall, which cleave the detectable group at each step.

Most significantly, however, the instant methods are more adaptable to full automation since the biopolymer is fully synthesized prior to quality control assessment and correction (deprotection steps) processing. A nearly 100% yield is critical in on-chip synthesis, since the option to merely separate and discard the still-protected oligonucleotides does not exist.

Wagner teaches use of dnseoc groups for base protection during oligonucleotide synthesis, asserting that it provides fast and effective cleavage at the monomeric as well as oligomeric levels. Applicants note, however, that although Wagner synthesizes oligonucleotides on solid supports, Wagner implements all quality control assessments after the oligos are removed from the support (see page 205, beginning with line 6, "The isolated samples were cleaved..."). Reverse phase HPLC was used to test deprotection. Polyacrylamide gel electrophoresis was used for purification. Critically, Wagner fails to teach or suggest the use of fluorescence at the base-couplings to monitor a degree of deprotection or for quality control purposes whatsoever. Wagner teaches dnseoc solely with regard to protection and teaches only that its use effectuates efficient cleavage. The use of a fluorescent label is disclosed only for detection of the oligo and not for quality control: "The starting nucleoside N (= 3-methylisoxanthopterin) was used as a fluorescence marker allowing direct detection by fluorescence determination", page 205, last sentence before Table 1. Wagner fails to teach or suggest methods for quality assessment or control that exploit a coupling a detectable protecting group at the nucleobase. Although the nucleobase protecting group of Wagner possesses fluorescent properties, Wagner fails to utilize or suggest utilization of the fluorescence for quality control purposes. Applicants submit that Wagner is directed to the discovery and implementation of dnseoc as a readily cleavable protection group for the base amine and is completely silent as to problems or solutions relating to on-chip quality control with respect to degree of deprotection of an oligonucleotide which may not be removed from the support for analysis.

Agris is also directed to solving the more simple problem in the art of oligonucleotide synthesis wherein the oligonucleotide is synthesized on a solid support but is thereafter removed from the support for its desired end use. This is similar to Wagner. While synthesis is on the solid support, analysis and assessment take place after cleavage via techniques known in the art such as HPLC and gel electrophoresis. Agris expressly notes that automated synthesis of oligonucleotides on solid supports includes the use of agents to protect the exocyclic amines of the nucleotide bases A, T, C, and G (U does not possess such an amine) and to block the hydroxyls of the RNA ribose.

Agris merely expresses the problems with the Wagner technology. Agris, in the context of off-support analysis, teaches that extent of base deprotection is "not easily determined." Agris does not address the problem or deficiency in the art addressed by the instant invention, which relates to synthesis of oligonucleotides on bio-chips where the end use of the oligonucleotide takes place on the chip and therefore wherein quality control and other post-synthetic analysis must likewise take place on the chip.

Agris relates generally to determination of degree of deprotection of synthetic oligonucleotides. Agris does not offer the practitioner any specific guidance relating to making that determination while the oligonucleotide remains bound (in an array that may include similar or dissimilar species) to the solid support on which it is synthesized (i.e., a bio-chip). The Agris methods, like the analytic methods of Wagner, result in consumption of the oligonucleotide being assayed.

The instant specification clarifies the distinction and unique challenges presented by on-chip synthesis. Quality of the produced oligonucleotide must be assessed while the oligonucleotide remains bound to the chip and must not result in consumption of the oligonucleotide. With respect to on-chip quality control, known methods involve covalent binding of a fluorescing material at the terminus of the oligonucleotide which can then be detected and quantified. In order for complete deprotection to be achieved, methods for assessing degree of deprotection with retention of yield and while the oligo remains bound are necessary. McGall offers an inferior solution.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000). The combination of McGall, Wagner, Agris, Hobbs and Chen fail to teach or suggest quality control methods relating to assessing degree of deprotection of a biopolymer synthesized and assessed on a chip wherein detectable protecting groups are coupled at the nucleobase amine and remain coupled until complete synthesis of the biopolymer. Although McGall relates to on-chip analysis with retention of yield, McGall is poorly adaptable to automation since assessment and correction are required after each addition of building blocks. Wagner teaches protection by dnseoc at the nucleobasc amine, but fails to assessment of deprotection and fails to relate it in any way to on -chip biopolymer synthesis. Agris expressly teaches that degree of deprotection of nucleobase amines is difficult. Hobbs and Chen are inapposite to the deficiencies of the primary references.

Claims 1-3, 12, 13, and 15-22 are therefore nonobvious and patentable under 35 USC §103 over McGall and Wagner in view of Agris, further in view of Hobbs and Chen. Reconsideration is therefore respectfully requested.

Conclusion

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 1-3, 12, 13, and 15-22 at an early date is earnestly solicited.

The Commissioner is hereby authorized to charge any fees associated with this Amendment to Deposit Account No. 02-2958.

Respectfully submitted,

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